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OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with N-nitrosodiphenylamine. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to October, 1985. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health ad Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria Document for Nitrosamines. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-064. NTIS PB81-117756.

U.S. EPA. 1986a. Health and Environmental Effects Profile for Nitrosamines. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope, which tended to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RFD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

N-Nitrosodiphenylamine administered to F344 rats in their diets for 100 weeks caused a significant increase in the incidence of bladder transitional cell carcinoma in both male and female rats (NCI, 1979). Using data from female rats, a human q_1^* of 4.92×10^{-3} $(mg/kg/day)^{-1}$ was calculated (U.S. EPA, 1980a).

No data concerning the potential carcinogenicity of N-nitrosodiphenylamine by inhalation exposure were located in the available literature; therefore, an inhalation q_1^* was not calculated.

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Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
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Editorial review for the document series was provided by the following:

Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office
Cincinnati, OH

Technical support services for the document series was provided by the following:

Bette Zwayer, Jacky Bohanon and Kim Davidson
Environmental Criteria and Assessment Office
Cincinnati, OH

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LIST OF ABBREVIATIONS

CAS	Chemical Abstract Service
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
K_{oc}	Soil sorption coefficient
MTD	Maximum tolerated dose
NOEL	No-observed-effect level
ppm	Parts per million
RfD	Reference dose
RfD_S	Subchronic reference dose
TWA	Time-weighted-average

1. ENVIRONMENTAL CHEMISTRY AND FATE

Selected chemical and physical properties and environmental fate of N-nitrosodiphenylamine are presented in Table 1-1.

In the atmosphere, N-nitrosodiphenylamine is expected to undergo rapid photolytic transformation. The atmospheric half-life of this compound is estimated to be <1 day based on estimated photolysis half-lives ranging from ~5-30 minutes for nitrosodimethylamine to several hours for N-nitrosodimethyl-, N-nitrosodiethyl and N-nitrosodi-n-propylamine (Cupitt, 1980; Hanst et al., 1977; Tuazon et al., 1984; Grosjean et al., 1978; Crosby et al., 1980).

In water, N-nitrosodiphenylamine is probably removed by photochemical transformation and volatilization. The half-life in water listed in Table 1-1 is the volatilization half-life from water 1 m deep. This value was calculated based on an estimated Henry's Law constant of 6.4×10^{-4} atm-m³/mol at 25°C using the method of Lyman et al. (1982). Relatively rapid photolysis of other nitrosamines in aquatic solutions (Polo and Chow, 1976; Burns and Alliston, 1971) suggests that photolysis of N-nitrosodiphenylamine would be a competitive removal process. An estimated K_{oc} value of 1202 suggests that N-nitrosodiphenylamine would adsorb significantly to suspended solids and sediments. Bioaccumulation in aquatic organisms should not be significant. The soil half-life listed in Table 1-1 is based on a study by Mallik and Tesfai (1981) in which 60% removal of 354 µg N-nitrosodiphenylamine/g unamended soil occurred in 30 days and complete removal in amended soil (17.5% organic matter content) occurred in 10 days. Since the experiments were performed in the absence of sunlight, the effect of photolysis was not determined. The estimated K_{oc} value suggests that N-nitrosodiphenylamine has low mobility in soil (Swann et al., 1983).

TABLE 1-1

Selected Chemical and Physical Properties and Environmental Fate of N-Nitrosodiphenylamine

Property	Value	Reference
CAS number:	86-30-6	
Chemical class:	aromatic nitrosamine	
Molecular weight:	198.22	
Vapor pressure: at 25°C	0.1 mm Hg	Mabey et al., 1981
Water solubility: at 25°C	40 mg/ℓ	Mabey et al., 1981
Log octanol/water partition coefficient:	3.13	Hansch and Leo, 1985
Bioaccumulation factor:	217, bluegill sunfish (Lepomis macrochirus)	Barrows et al., 1980
Soil adsorption coefficient:	1202 (estimated)	Lyman et al., 1982
Half-lives in		
Air:	<1 day (estimated)	
Water:	11 hours (estimated)	Lyman et al., 1982
Soil:	<22 days	Mallik and Tesfai, 1981

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

Pertinent quantitative data regarding the absorption of N-nitrosodiphenylamine by either the oral or inhalation routes of exposure could not be located in the available literature. It can be inferred from systemic toxic effects observed after oral exposure that N-nitrosodiphenylamine is absorbed by the gastrointestinal tract. No inhalation studies were located.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. NCI (1979) performed subchronic dietary studies with groups of five male and five female F344 rats and equal numbers of B6C3F1 mice in order to determine the MTD for the chronic carcinogenicity experiment. These subchronic studies lasted 11 weeks for male rats and 8 weeks for female rats, male mice and female mice. Parameters of toxicity evaluated were survival, body weight, gross appearance at necropsy and a limited histopathological examination of unspecified organs and tissues. Male rats were fed diets containing 1000-10,000 ppm n-nitrosodiphenylamine and female rats were fed diets containing 4000-46,000 ppm. All male rats survived and body weights at termination were depressed $\geq$10%, relative to controls at $\geq$4000 ppm. In female rats, diets $\geq$16,000 ppm resulted in mortality, and terminal body weight depression >10% was observed at 4000 ppm, the lowest dietary concentration tested.

In the first of two 8-week studies using mice, both sexes were fed diets containing 3160-14,700 ppm N-nitrosodiphenylamine (NCI, 1979). All mice survived and body weights appeared to be unaffected. In the second experiment, male mice received diets containing 4250-22,000 ppm and female mice received diets containing 22,000-46,000 ppm; all mice survived. The threshold for a 10% depression in terminal body weight relative to controls appeared to be at 9500-15,000 ppm for male mice and 46,000 ppm, the highest dietary concentration tested, for female mice. Gross examination at necropsy revealed no abnormalities in either species. The only histopathological lesion observed was a trace of pigmentation in the Kupffer cells in the livers of female mice at 46,000 ppm.

3.1.2. Inhalation. No pertinent data regarding the subchronic inhalation toxicity of N-nitrosodiphenylamine were located in the available literature.

3.2. CHRONIC

3.2.1. Oral. NCI (1979) reported the chronic effects of N-nitrosodiphenylamine (98% pure) in rats and mice in a carcinogenicity experiment. Groups of 50 male and 50 female 6-week-old F344 rats and 50 male and 50 female 6-week-old B6C3F1 mice were fed N-nitrosodiphenylamine in their diets. Rats were fed 1000 or 4000 ppm of the compound in their diet for 100 weeks and male mice were fed diets containing 10,000 or 20,000 ppm for 101 weeks. Female mice were started on diets containing 5000 or 10,000 ppm, but at 38 weeks, because of excessive depression of mean weight gain, treatment was discontinued for 3 weeks and dietary concentrations were changed to 1000 or 4000 ppm for 60 weeks. The TWA dietary concentrations for the low- and high-dose female mice were 2475 and 6139 ppm, respectively. Controls consisted of 20 rats/sex and 20 mice/sex that were given untreated diets. The chronic effects observed in rats were higher incidences of corneal opacity in high-dose males (15/50) and low-dose females (15/50) than in corresponding control groups (males 0/20; females 1/20). Epithelial hyperplasia of the bladder was also observed in treated rats but not in controls [male, 0/19 (control), 2/46, 6/45; female, 0/18 (control), 4/48, 7/49]. In mice, submucosal inflammation of the urinary bladder was observed in treated groups of both sexes. Incidences in the control, low-dose and high-dose groups were 0/18, 12/49 and 31/48, respectively, in males and 0/20, 31/49 and 30/38, respectively, in females. Epithelial hyperplasia of the bladder also occurred at low incidences in treated mice [male, 0/20 (control), 2/49, 7/46; female, 0/18 (control), 3/47, 5/38].

3.2.2. Inhalation. No pertinent data regarding chronic effects of N-nitrosodiphenylamine following inhalation exposure were located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding teratogenicity and other reproductive effects of N-nitrosodiphenylamine following oral or inhalation exposure could not be located in the available literature.

3.4. TOXICANT INTERACTIONS

Pertinent data regarding the interaction of N-nitrosodiphenylamine with other toxicants could not be located in the available literature.

4. CARCINOGENICITY

4.1. HUMAN DATA

Pertinent data regarding the carcinogenic potential of N-nitrosodiphenylamine by either the oral or inhalation routes of exposure could not be located in the available literature.

4.2. BIOASSAYS

4.2.1. Oral. In the NCI (1979) study, groups of fifty 6-week-old F344 rats/sex were fed diets containing 1000 or 4000 ppm N-nitrosodiphenylamine for 100 weeks. Groups of fifty 6-week-old B6C3F1 male mice were fed diets containing 10,000 or 20,000 ppm of the compound, while groups of 50 female mice were fed diets containing a TWA concentrations of 2475 or 6139 ppm (see Section 3.2.1.) for 101 weeks. Matched controls consisted of 20 rats/sex and 20 mice/sex given untreated diets. Comprehensive pathological examinations were conducted on all moribund animals, survivors and animals that died during the study, unless precluded by autolysis or cannibalization.

All treated mice had decreased body weight gain, but mortality was not significantly affected by treatment. Tumor incidences and types of tumors in treated mice were similar to those of controls. Submucosal inflammation and epithelial hyperplasia of the bladder occurred in treated mice of both sexes (see Section 3.2.).

Compared with the corresponding controls, all treated groups of male and female rats showed lower mean body weights, which were dose-related in males throughout the experiment and became dose-related for females between weeks 40 and 68 (body weights were not recorded during this period). Mortality was dose-related in female rats ($p=0.024$) but not in males. At termination, survival substantially below that of controls occurred only in high-dose females. In both sexes of rats, a statistically increased incidence

($p<0.001$) of transitional cell carcinoma of the urinary bladder was observed in the high-dose group. Incidences are presented in Table 4-1. Fibromas of the integumentary system also occurred in male rats at incidences (1/19, 1/46 and 10/45 in control, low- and high-dose males, respectively) that were dose-related ($p<0.003$), but not significantly higher than those in the control group. When compared with historical controls from the same laboratory that have an incidence of integumentary system fibromas of 6/285, these results suggest an association of the fibromas with treatment.

Other carcinogenicity bioassays of N-nitrosodiphenylamine have not shown statistically significant increases in tumor incidences. Druckrey et al. (1967) gave N-nitrosodiphenylamine to 20 BD rats of unspecified sex in drinking water at a daily dose of 120 mg/kg (total dose 65 g/kg). No tumors were observed within 700 days. Additional details were not available.

Argus and Hoch-Ligeti (1961) treated 25 male Wistar rats by gavage with 1.07 mg N-nitrosodiphenylamine in 1 ml of 1% aqueous methylcellulose, 5 days/week for 45 weeks (244 mg/rat = total dose). The rats were killed at 53 weeks. No tumors were observed in any rats by gross or histological examination. The dose given may have been too low to induce tumors within the observation period.

BRL (1968) and Innes et al. (1969) studied the potential carcinogenicity of N-nitrosodiphenylamine in B6C3F1 and B6AKF1 mice. Commercial grade N-nitrosodiphenylamine was given to groups of 18 mice/sex/strain daily by gavage at 1000 mg/kg from 7-28 days of age, followed by 3769 ppm in the diet until 81 weeks (B63CF1 mice) and 83 weeks (B6AKF1 mice) of age. At the end of the treatment period, 12 male and 15 female B6C3F1 mice and 18 male and 17 female B6AKF1 mice had survived. Pathological and histological examinations were conducted on selected tissues (chest contents, liver, spleen,

TABLE 4-1

Carcinogenic Potency of N-Nitrosodiphenylamine (98% pure)
Administered in the Diet to F344 Rats[a]

Sex	Dose (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Target	Tumor Type	Tumor Incidence (p value)
M	0	100	100	bladder	transitional cell carcinoma	0/19 ($p<0.001$)[b]
M	1000	100	100	bladder	transitional cell carcinoma	0/46 (NS)
M	4000	100	100	bladder	transitional cell carcinoma	15/45 ($p\leq0.001$)[c]
F	0	100	100	bladder	transitional cell carcinoma	0/18 ($p<0.001$)[b]
F	1000	100	100	bladder	transitional cell carcinoma	0/48 (NS)
F	4000	100	100	bladder	transitional cell carcinoma	40/49 ($p<0.001$)[c]

[a]Source: NCI, 1979

[b]Cochran-Armitage Test for linear trend

[c]One-tailed Fisher Exact Test

NS = Not statistically significant

kidneys, adrenals, stomach, intestines and genitals) of survivors. No statistically significant ($p<0.05$) increases in tumor incidences were observed in the treated groups.

The lack of evidence of carcinogenicity in gavage and drinking water studies may be the result of differences in the method of oral exposure, dose, duration of treatment or length of observation period. NCI (1979) noted that the actual mechanism of bladder tumor induction is not known, but that one possible mechanism is by the nitrosation of amines in food.

4.2.2. Inhalation. Pertinent data regarding the carcinogenic potential of N-nitrosodiphenylamine following inhalation exposure could not be located in the available literature.

4.3. OTHER RELEVANT DATA

In a skin-painting study by Iversen (1980), groups of 16 male and 24 female hairless hr/hr Oslo strain mice were treated in the intrascapular region with single weekly applications of 0.1 ml of a 1% solution of N-nitrosodiphenylamine for 20 weeks. Mice surviving 80 weeks (14 males, 21 females) were necropsied, but the necropsy included only palpable lesions and histological examinations of the lungs. The only tumors observed were lung adenomas in three males. Control groups were not used in this study, although the author indicated that lung adenomas in the past were observed in dermal studies only after treatment with known carcinogens.

BRL (1968) injected groups of 18 B6C3F1 and 86AKF1 mice of each sex subcutaneously with N-nitrodiphenylamine in DMSO. Mice were injected in the nape of the neck with a single dose (1000 mg/kg) at ~28 days of age and were observed for ~18 months. Pathological and histological examinations were conducted on selected tissues (chest contents, liver, spleen, kidneys, adrenals, stomach, intestines and genitals) of survivors. The incidence of

reticulum cell sarcoma in male B6C3F1 treated mice was significantly increased (4/16 vs. 0/24 in the vehicle-treated control group). Increased incidences of reticulum cell sarcoma were not observed in female mice of either strain.

Boyland et al. (1968) gave groups of 24 male CB rats (6-7 weeks of age) weekly intraperitoneal injections of 2.5 mg N-nitrosodiphenylamine in polyethylene glycol 400, or vehicle only, for 6 months. Treatment-related tumors were not observed in the 5 treated and 10 control rats that survived 18-24 months.

N-Nitrosodiphenylamine has been found to be negative in numerous mutagenicity screening assays. IARC (1982) reviewed these studies and reported that N-nitrosodiphenylamine was negative in reverse/forward mutation repair assays in bacteria (E. coli, S. typhimurium) strains TA98, TA100, TA1535, TA1536, TA1537, TA1538, G46, C3076 and D3052), gene mutation and recombinogenicity assays in yeast and mutation assays with mouse lymphoma L5178Y/TK+/- cells and Chinese hamster V79 and ovary cells. N-Nitrosodiphenylamine was also negative for sex-linked recessive lethal mutations in D. melanoganter (Vogel et al., 1981), chromosomal aberrations in rat liver cells in vitro (Dean, 1981), sister chromatid exchange in Chinese hamster cells (Neal and Probst, 1983) and in micronucleus assays (Salamone et al., 1981).

N-Nitrosodiphenylamine tested positive in several in vitro assays with the yeast S. cerevisiae, including a reversion assay in strain XV185-14C, DNA repair assay in red mutant strain and in a test for mitotic aneuploidy in strain D6 (deSerres and Hoffman, 1981). The compound was also positive in unscheduled DNA synthesis in rat hepatocytes (Althaus et al., 1982) and alkaline elution tests also using rat hepatocytes (Sina et al., 1983).

Results in various cell transformation tests in mammalian systems were somewhat contradictory. Transformations in Syrian hamster embryo cells (Pienta and Kawalek, 1981), in BHK cells (Daniel and Dehnell, 1981) and F344 rat embryo cells infected with Rauscher murine leukemia virus (Dunkel et al., 1981) were induced by N-nitrosodiphenylamine. Styles (1981) and Dunkel et al. (1981), however, did not observe N-nitrosodiphenylamine-induced transformations in BHK cells, Sryian hamster embryo cells or Balb/373 cells.

4.4. WEIGHT OF EVIDENCE

Although drinking water and gavage studies of N-nitrosodiphenylamine (see Section 4.3.) have not demonstrated a carcinogenic effect, a significant increase in bladder transitional cell carcinoma was observed in F344 rats fed N-nitrosodiphenylamine in their diets (NCI, 1979). In the NCI (1979) study, groups of 50 F344 rats of each sex were fed 0, 1000 or 4000 ppm N-nitrosodiphenylamine in their diets for 100 weeks. The significant increase in bladder transitional cell carcinoma was observed in both sexes.

The evidence that N-nitrosodiphenylamine is carcinogenic in rats combined with a structure-activity relationship with other carcinogenic nitroso compounds is sufficient to classify the compound in IARC Group 2B, sufficient evidence for carcinogenicity in experimental animals, and place it in EPA Group B2 (U.S. EPA, 1986b).

5. REGULATORY STANDARDS AND CRITERIA

No occupational guidelines or standards for N-nitrosodiphenylamine are available from ACGIH, NIOSH or OSHA.

U.S. EPA (1980a) derived an ambient water quality criterion of 49 µg/ℓ for N-nitrosodiphenylamine, based on a q_1^* of 4.92×10^{-3} $(mg/kg/day)^{-1}$. This estimate of carcinogenic potency was based on the incidence of transitional cell carcinomas in the bladders of female rats in the NCI (1979) cancer study. The criterion is based on the level in water with consumption of 2 ℓ of water and 6.5 g of fish and shellfish associated with an excess cancer risk of 10^{-5}.

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S) AND REFERENCE DOSE (RfD)

N-Nitrosodiphenylamine has been shown to be a carcinogen in rats (NCI, 1979); therefore, no RfD or RfD_S will be calculated.

6.2. CARCINOGENIC POTENCY (q_1^*)

6.2.1. Oral. In the NCI (1979) bioassay, male and female F344 rats fed N-nitrosodiphenylamine in the diet showed significantly increased incidences of bladder transitional cell carcinoma. The U.S. EPA (1980a) used the incidence of bladder carcinoma in females to calculate a human q_1^* of 4.92×10^{-3} $(mg/kg/day)^{-1}$ for N-nitrosodiphenylamine. The data used in the derivation of this q_1^* are presented in Table 6-1.

6.2.2. Inhalation. Pertinent data regarding the carcinogenic potential of N-nitrosodiphenylamine following inhalation exposure could not be located; therefore, an inhalation q_1^* will not be derived.

TABLE 6-1

Cancer Data Sheet for Derivation of q_1^*
for N-Nitrosodiphenylamine

Compound: N-Nitrosodiphenylamine

Reference: NCI, 1979

Species/Strain/Sex: rat/F344/female

Route/vehicle: oral, diet

Length of exposure (le): 700 days

Length of experiment (Le): 700 days

Lifespan of animal (L): 700 days

Body weight = 0.250 kg

Tumor type and site: bladder, transitional cell carcinoma

Dose (mg/kg/day)	Incidence No. Responding/No. Tested
0	0/18
50	0/48
200	40/49

Human q_1^* = 4.92×10^{-3} $(mg/kg/day)^{-1}$ derived by U.S. EPA (1980a) using linearized multistage model adopted by U.S. EPA (1980b).

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APPENDIX

Summary Table for N-Nitrosodiphenylamine*

Route	Species/ Strain/ Sex	Experimental Exposure/Dose (mg/kg/day)	Effect	Human q_1^* $(mg/kg/day)^{-1}$
Oral	rat/ F344/F	0 50 200	transitional cell carcinoma of bladder	4.92×10^{-3}

*Source: NCI, 1979; U.S. EPA, 1980a, 1986a